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Vaccination with the CHAT Strain of Type 1 Attenuated Poliomyelitis Virus in Léopoldville, Belgian Congo*

2. Studies of the Safety and Efficacy of Vaccination

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In the course of the attenuated live poliovirus vaccination trial described in the preceding paper, an estimated 46 000 African children were given CHAT strain. Among the 3400 children followed up by home visits, none developed paralytic poliomyelitis or aseptic meningitis. When bled 2-3 months after vaccination, 60% of previously type-1 negative children had antibodies; interference by wild enteric viruses is suggested in explanation of this low figure.

Two months after the beginning of vaccination, a type-1 poliomyelitis epidemic broke out, largely concentrated in a district in which no vaccination had yet been done. No geographical, chronological or family association between vaccination and poliomyelitis cases could be found. Of a total of 99 cases, 10 were in vaccinated children; but the intervals between vaccination and onset and identification of viruses from patients indicated that no case was caused by the vaccine.

Previous vaccination with CHAT virus appeared to confer significant protection (60%) against the epidemic type 1 strain.

A campaign of vaccination with the CHAT type 1 attenuated poliovirus of Koprowski (1957) was begun in Léopoldville, Belgian Congo, on 18 August 1958. The history of poliomyelitis in Léopoldville, the considerations which led to the use of living virus, and the development and design of the vaccination campaign have been presented in the preceding article (see page 203). The present paper is concerned with the progress of the trial up to 30 April 1959, by which date over 45 000 children had been vaccinated. The results of serological studies and of post-vaccination health inquiries are given, and cases of paralytic poliomyelitis occurring in Léopoldville after the beginning of the campaign are analysed with regard to the safety and efficacy of the vaccine.

MATERIALS AND METHODS

These are described in the first paper of this series (see page 204) and will not be further considered.

THE RESULTS OF THE VACCINATION CAMPAIGN

As discussed in the preceding paper, vaccination was limited to children under 5 years of age, as the morbidity data showed that paralytic poliomyelitis was concentrated in this age-group. The numbers of such children, according to the medical census, are given for the seven districts of the city in Table 1. There was a total of approximately 76 200 African children eligible for vaccination in metropolitan Léopoldville, 40 000 of whom were 6 months to 3 years old.

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TABLE 1
VACCINATION WITH CHAT VIRUS THROUGH 30 APRIL 1959 BY DISTRICT OF LÉOPOLDVILLE

District	Children 6 months—2 years (in thousands)	Children under 5 years (in thousands)	Number vaccinated (under 5 years)
Ancienne Cité	13.5	24.8	19 182
Nouvelle Cité	15.1	29.0	12 647
Ndjili	3.8	7.2	4 347
Matete	2.9	5.4	3 745
Kintambo	2.5	4.7	2 885
Bandalungwa	2.1	3.9	1 735
Camp Léopoldville	0.7	1.2	1 185
Totals	40.6	76.2	45 726

The cumulative totals of vaccinated individuals for each week by district are given in Table 2. For geographical orientation, the map of Léopoldville given by Lebrun and co-authors on page 206 of this issue should be consulted. It can be seen that the campaign was confined to the smaller districts of the city—Kintambo, Ndjili, Matete, Bandalungwa, and Camp Léopoldville—during the first nine weeks of vaccination. Small numbers of children from the larger Ancienne and Nouvelle Cités were vaccinated at the end of October and the beginning of November, respectively, and larger numbers thereafter.

At 30 April 1959, 45 726 children had received CHAT virus; the number by district is shown in Table 1. The age distribution of vaccinees is shown in Table 3: the largest group was under 1 year of age, the smallest was 4 years old, with intermediate numbers in the other age-groups. The division of the age-group under 1 year old into those infants less than 6 months and those 6-11 months had to be estimated because this distinction was not consistently recorded. However, inasmuch as 89% of this group was vaccinated, its age distribution could be estimated with reasonable confidence from the distribution of infants in the general population. The partial data which were available from vaccination records agreed with the predicted distribution quite closely.

Serological studies

Over 1300 sera were obtained before vaccination from children 6 months to 4 years old during the early stages of the campaign (August to early November 1958). All districts except the Nouvelle Cité were represented in the sample.

The sera were tested at a 1 : 4 dilution in the metabolic inhibition test (Lipton & Steigman, 1955). No significant differences were seen between sera from residents of the African and the European types of housing area; for example, the percentage of positive sera from infants 6 months to 1 year old was 9% in the Ancienne Cité and 12% in the European-style Matete district. All the results were therefore combined in Table 4 and Fig. 1. Type 1 poliomyelitis antibodies were found in the sera of 9% of children 6-11 months old, 23% of 1-year-olds, 46% of 2-year-olds, 67% of 3-year-olds, and 90% of 4-year-olds. The percentages of children with type 2 and type 3 antibodies similarly increased with age: type 3 antibodies, however, were found more often than type 1 in children during the first three years of life, whereas type 2 antibodies were found less frequently up to the age of 4 years. The percentage of children with no antibodies to any of the three types of poliovirus—" triple negatives " —decreased from 74% of those 6-11 months to zero among those 4 years of age.

FIG. 1
SERO-IMMUNITY TO POLIOMYELITIS OF LÉOPOLDVILLE AFRICAN CHILDREN, AS DETERMINED BY TESTS ON OVER 1300 SERA

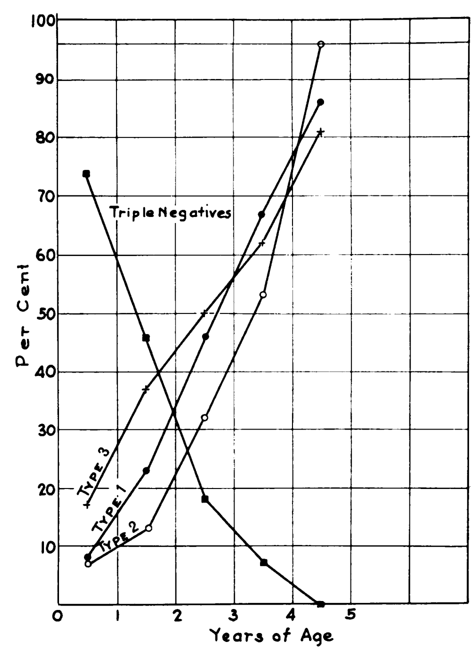


TABLE 2
PROGRESS OF VACCINATION WITH CHAT VIRUS IN LÉOPOLDVILLE

Weeks beginning:	Cumulative totals of vaccinations by district (in thousands)								Vaccination centres in use [a]
	Kintambo	Ndjili	Matete	Banda-lungwa	Camp Léopoldville	Ancienne Cité	Nouvelle Cité	All	
1958 Aug. 18	1.5	—	—	—	—	—	—	1.5	A
25	1.9	0.5	—	—	—	—	—	2.5	C
Sept. 1	1.9	0.5	—	—	—	—	—	2.5	
8	1.9	3.5	0.8	—	—	—	—	6.3	C, D
13	1.9	3.5	2.4	—	—	—	—	7.9	D
22	1.9	3.5	2.4	1.0	—	—	—	8.9	E
29	1.9	3.5	2.4	1.0	—	—	—	8.9	
Oct. 6	1.9	3.5	2.4	1.0	0.8	—	—	9.7	F
13	1.9	3.5	2.4	1.0	0.8	—	—	9.7	
20	1.9	3.5	2.4	1.0	0.8	0.2	—	10.0	G
27	1.9	3.5	2.4	1.0	0.8	0.4	—	10.2	H, I
Nov. 3	1.9	3.6	2.4	1.0	0.8	1.0	0.1	11.0	I, J, K, Y
10	2.0	3.6	2.4	1.1	0.8	1.3	0.3	11.4	K, Y
17	2.0	3.6	2.4	1.1	0.8	1.6	0.4	12.0	K, Y
24	2.0	3.6	2.5	1.1	0.8	2.0	0.6	12.5	K, Y
Dec. 1	2.0	3.7	2.5	1.1	0.8	2.7	0.8	13.7	L, M, N, Y
8	2.1	3.8	2.5	1.2	1.2	3.6	1.2	15.5	L, N, O, P, Y
15	2.1	3.8	2.6	1.2	1.2	4.5	1.5	16.9	L, N, Y
22	2.1	3.9	2.6	1.2	1.2	4.7	1.7	17.3	L, N, Y
29	2.1	3.9	2.6	1.2	1.2	5.0	2.0	18.0	R, Y
1959 Jan. 5	2.1	3.9	2.6	1.2	1.2	5.1	2.1	18.3	Y
12	2.2	3.9	2.6	1.3	1.2	5.4	2.2	18.7	Y
19	2.2	4.0	2.7	1.3	1.2	6.3	3.1	20.8	Y
26	2.3	4.0	2.8	1.4	1.2	6.6	3.4	21.6	S, Y
Feb. 2	2.3	4.0	2.8	1.4	1.2	7.4	4.6	23.7	T, U, Y
9	2.3	4.0	2.9	1.4	1.2	8.8	5.3	25.9	S, T, U, Y
16	2.4	4.1	2.9	1.4	1.2	11.8	6.0	29.2	B, S, T,U, Y
23	2.5	4.1	3.0	1.5	1.2	12.7	6.7	31.6	B, T, U, X, Y
March 2	2.6	4.1	3.0	1.5	1.2	14.1	7.5	34.0	B, U, X, W, Y
9	2.6	4.1	3.1	1.6	1.2	14.9	8.2	35.7	U, V, W, X, Y
16	2.7	4.2	3.1	1.6	1.2	15.5	8.9	37.1	X, V, W, Y
23	2.7	4.2	3.1	1.6	1.2	16.4	9.5	38.7	X, V, Y
30	2.8	4.2	3.2	1.6	1.2	17.2	10.1	40.2	X, Y
April 6	2.8	4.2	3.2	1.6	1.2	17.5	10.4	41.0	Y
13	2.8	4.3	3.3	1.7	1.2	18.0	10.8	42.0	Y
20	2.8	4.3	3.5	1.7	1.2	18.7	11.9	44.0	Y
27	2.9	4.3	3.7	1.7	1.2	19.2	12.6	45.7	Y

[a] Locations shown in Fig. 3, 6, and 7

TABLE 3
AGE DISTRIBUTION AND SUSCEPTIBILITY OF VACCINATED POPULATION

Age (years)	Number vaccinated	Estimated No. of type 1 negative vaccinated [a] (in thousands)	Estimated No. of triple non-immunes vaccinated [a] (in thousands)
<1	14 924	—	—
<½	7 600 [b]	NT	NT
½-	7 300 [b]	6.7	5.4
1–	10 340	8.0	4.8
2–	7 827	4.2	1.4
3–	7 027	2.3	0.5
4–	5 608	0.6	—
Totals	45 726	21.8	12.1

[a] For serological percentages see Table 4.
[b] Estimated from demographic data and partially known age partition of the vaccinated (see text).
NT = Not tested

Thus the results of the survey indicated that sero-immunity to poliomyelitis is acquired by African children in Léopoldville usually within the first five years of life, but that a large percentage of infants under 3 years lack antibodies.

Three hundred and forty children vaccinated in August to November 1958, who were found to be without type 1 antibodies before vaccination, were re-bled 3 months later (November 1958 to late January 1959). Of these, only 60% had developed type 1 neutralizing antibodies during the interval (Table 5). Slight differences were noted in the results from different districts, but these were statistically insignificant. Heterotypic poliomyelitis antibodies had developed during the same period at a rate of 7% each for types 2 and 3. Of 62 non-vaccinated individuals who were bled in October 1958 and re-bled in January 1959, 35% had acquired type 1 antibodies in the three-month interval (Table 5).

Studies of safety, including post-vaccination inquiries

As described in the preceding article (see page 203), in addition to epidemiological surveillance of the population a system of post-vaccination inquiries was employed in order to obtain data concerning the safety of the CHAT virus.

Thus, 7645 children from all districts of Léopoldville were registered at vaccination for follow-up; of these 7311 were seen 8 days after vaccination, and 7195 were seen 15 days after vaccination. The difference between the first two figures was due to incorrect addresses, and the difference between the second and third figures was the result of families having moved.

The age distribution of children on whom post-vaccination inquiries were completed, shown in Table 6, was markedly shifted towards infancy: 59% of the children on whom inquiries were made were less than 1 year of age.

TABLE 4
ANTIBODIES TO POLIOMYELITIS IN SERA OF LÉOPOLDVILLE AFRICAN CHILDREN

(Age years)	Antibodies to poliovirus											
	Type 1			Type 2			Type 3			No type [a]		
	No. tested	No. pos.	% pos.	No. tested	No. pos.	% pos.	No. tested	No. pos.	% pos.	No. tested	No. neg. [b]	% neg.
½–	411	35	9	350	23	7	375	64	17	340	251	74
1–	615	139	23	553	71	13	579	213	37	536	248	46
2–	199	92	46	172	55	31	188	95	51	165	29	18
3–	52	35	67	45	24	53	48	29	60	44	3	7
4–	41	37	90	25	24	96	26	21	81	24	0	0
Totals	1 318	338	26	1 145	197	17	1 216	402	33	1 109	531	48

[a] Triple negatives [b] For all three types

TABLE 5

POLIOMYELITIS ANTIBODIES AFTER CHAT VIRUS VACCINATION [a]

Age (years)	Type 1 No. tested	Type 1 % pos.	Type 2 No. tested	Type 2 % pos.	Type 3 No. tested	Type 3 % pos.
Vaccinated:						
½–	105	56	30	13	29	0
1–	182	64	54	2	52	6
2–	45	56	9	22	11	27
3–	8	63	2	0	2	50
Totals	340	60	95	7	94	7
Non-vaccinated:						
½–	38	32	24	13	25	4
1–	24	42	11	9	12	8
Totals	62	35	35	11	37	5

[a] All sera were previously negative for the type indicated.

TABLE 7

ILLNESSES RECORDED ON POST-VACCINATION INQUIRIES

Illness category	During week before vaccination No.	During week before vaccination % of total	First week after vaccination No.	First week after vaccination % of total	Second week after vaccination No.	Second week after vaccination % of total
Upper respiratory	374	4.9	563	7.7	590	8.2
Digestive	126	1.7	208	2.9	213	3.0
Skin and mucosal	39	0.5	70	1.0	51	0.7
Fever	14	0.2	54	0.7	32	0.4
Lower respiratory	9	0.1	17	0.2	21	0.3
Anaemia	19	0.2	25	0.3	24	0.3
Miscellaneous	8	0.1	31	0.4	39	0.5
All illnesses	589	7.7	968	13.2	970	13.5
No symptoms	7 056	92.3	6 343	86.8	6 225	86.5
Totals	7 645	100.0	7 311	100.0	7 195	99.9

The illnesses reported to the nurses on the health inquiries are analysed in Table 7 according to the class of illness and the time of inquiry. On the first inquiry, conducted on the day of vaccination, 589 illnesses were reported to have occurred during the preceding week. On the second and third inquiries, 8 and 15 days after vaccination, 968 and 970 illnesses were reported.

None of the 2527 recorded illnesses were paralytic poliomyelitis or aseptic meningitis. The largest class of illnesses was upper respiratory disorders, with gastro-intestinal complaints second.

Serious illnesses (listed in the category " Miscellaneous " in Table 7) discovered on post-vaccination inquiry are listed in Table 8. The single neurological

TABLE 6

AGE DISTRIBUTION AND SUSCEPTIBILITY OF CHILDREN IN WHOM POST-VACCINATION INQUIRIES WERE MADE

Age (years)	No. of inquiries completed	Estimated type 1 negative [a] (in thousands)	Estimated triple non-immunes [a] (in thousands)
<1	2 980	—	—
<½	1 520 [b]	NT	NT
½–	1 460 [b]	1.3	1.1
1–	1 611	1.2	0.7
2–	852	0.5	0.2
3–	979	0.3	0.1
4–	773	0.1	—
Totals	7 195	3.4	2.1

[a] For serological percentages, see Table 4.

[b] Estimated from geographical data and partially known age partition of the vaccinated (see text).

NT = Not tested.

TABLE 8

MISCELLANEOUS ILLNESSES DISCOVERED ON POST-VACCINATION INQUIRIES

Illness	Number
Varicella	42
Rubeola	14
Mumps	3
Otitis	4
Malaria	3
Infection at venipuncture site	1
Retropharyngeal abscess	1
Fatal pneumonia	1
Encephalitis	1

illness was a case of "encephalitis" in a 4-year-old girl, who developed fever, profound somnolence, and paraplegia 16 days after ingesting CHAT virus. She was admitted to the Contagious Diseases Hospital, where a neurological consultant found spastic paralysis of both legs with positive Babinski signs and hyperreflexia. A lumbar puncture revealed normal cerebrospinal fluid. The consultant's diagnosis was acute encephalitis. The child was also seen by one of the present authors in May 1959, eight months subsequent to the acute illness. At this time she walked with a "scissors" gait and was without evidence of muscular weakness or atrophy. Hyperreflexia persisted, and the child had difficulty in speech. It was concluded that this illness was not caused by poliomyelitis infection.

The total rate of reported illness was 8% in the week before vaccination and 13% in each of the two weeks following vaccination ($\chi^2=152$; $n=2$; $P=<0.01$). It is important to note, however, that the incidence of illnesses presumably unrelated to vaccination, for example, "upper" and "lower respiratory", "skin and mucosal", and "anaemia", also increased by 50%-100% over the pre-vaccination figures. This difference was also significant ($\chi^2=86.6$; $n=6$; $P=<0.01$).

An attempt was made to estimate the number of susceptibles vaccinated and the number submitted to follow-up examination. The analysis by age-group of vaccinations and of post-vaccination inquiries has been given in Tables 3 and 6. The number in each group was then multiplied by the percentages of type-1 negative or of triple-negative individuals found in the serological survey (Table 4). It will be noted that no sera were obtained from infants below 6 months of age, and therefore no statement about their susceptibility was possible.

Thus the estimate of type-1 non-immunes vaccinated was 21 800, of whom about 12 100 were triple negatives (Table 3). Similarly, about 3400 type-1 seronegative infants were followed after vaccination, of whom probably 2100 were triple negatives (Table 6).

PARALYTIC POLIOMYELITIS IN LÉOPOLDVILLE DURING THE VACCINATION CAMPAIGN

As discussed in the preceding paper (see page 203) poliomyelitis is both endemic and epidemic in Léopoldville and other parts of the Belgian Congo. In Table 9 is given the reported number of cases from the city and province of Léopoldville during the eight months of 1958 just prior to the vaccination campaign. In the city, 23 cases occurred during January to March 1958, which represented the end of an epidemic that had begun in November 1957. In Léopoldville province, exclusive of the city, 41 cases of paralytic poliomyelitis were reported from June to August 1958. Type 1 poliovirus was isolated from the stools of some of these patients, and serological studies showed recent activity of this agent.

TABLE 9
REPORTED POLIOMYELITIS CASES BY MONTH, LÉOPOLDVILLE CITY AND PROVINCE, JANUARY-AUGUST 1958

Month	City	Province (excluding city)
January	12	11
February	5	1
March	6	6
April	1	7
May	2	1
June	0	12
July	1	19
August	0	11

An epidemic of 99 cases of paralytic poliomyelitis, including 4 deaths, broke out in Léopoldville city at the end of October 1958, two months after the commencement of vaccination. The epidemic reached its peak in December 1958 and ended in March 1959 (Fig. 2).

FIG. 2
MONTHLY TOTALS OF REPORTED CASES OF PARALYTIC POLIOMYELITIS OCCURRING AMONG AFRICANS IN LÉOPOLDVILLE FROM AUGUST 1958 THROUGH APRIL 1959

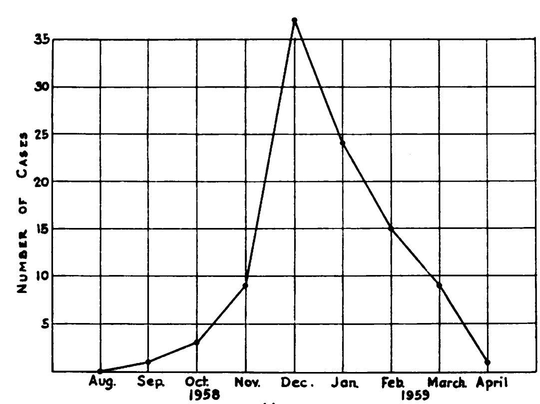


TABLE 10

1958-59 EPIDEMIC CASES OF POLIOMYELITIS ANALYSED BY AGE AND COMPARED TO PREVIOUS YEARS

Age (years)	Jan. 1956-July 1958		Aug. 1958-April 1959	
	No.	%	No.	%
< 1	54	32	25	25
1–	82	49	57	58
2–	17	10	15	15
3–	5	3	1	1
4–	1	1	—	—
> 5	8	5	1	1
Totals	167 [a]	100	99	100

[a] Three additional cases without age specified.

TABLE 11

DISTRIBUTION OF PARALYSIS IN 1958-59 EPIDEMIC CASES COMPARED TO PREVIOUS YEARS

Site of paralysis	Jan. 1956-July 1958		Aug. 1958-April 1959	
	No.	%	No.	%
One leg	79	56	52	54
Both legs	49	35	32	33
Arms and legs	9	6	10	10
One arm	2	1	—	—
Bulbar	2	1	2	2
Totals	141 [a]	99	96 [b]	99

[a] Three additional cases without information.
[b] Twenty-nine additional cases without information.

The age distribution of the paralytic cases is given in Table 10; as in the past, the greatest number of patients were 1-year-olds, and over 90% were under 3 years of age. The clinical localization of paralysis (Table 11) was also quite similar to that observed in the past, with involvement of the lower extremities exclusively occurring in over 85% of cases.

Examination of the geographical localization of the cases revealed a distinct difference between the 1958-59 epidemic and the experience from 1951 through July 1958. As shown in Table 12, the greatest number of cases in past years had occurred in children living in the Ancienne Cité, with only two-thirds as many cases in children in the Nouvelle Cité. However, in the 1958-59 epidemic, which is analysed in Table 13, the ratio was reversed and the cases in the Ancienne Cité numbered two-thirds of those in the Nouvelle Cité.

TABLE 12

CASES OF PARALYTIC POLIOMYELITIS BY DISTRICT OF LÉOPOLDVILLE, 1951-58

District	Reported cases by year								Total	
	1951	1952	1953	1954	1955	1956	1957	1958 [a]	No.	% of all cases
Ancienne Cité	25	35	30	8	39	30	27	9	203	(46.2)
Nouvelle Cité	15	20	27	5	17	22	22	6	134	(30.5)
Camp Léopoldville	9	2	2	—	2	4	1	—	20	(4.6)
Kintambo	3	2	—	—	6	4	5	3	23	(5.2)
Matete [b]				1	6	5	2	3	17	(3.9)
Ndjili [b]					2	9	3	1	15	(3.4)
Bandalungwa [b]						1	2	2	5	(1.1)
Unknown	2	6	2	1	2	3	3	3	22	(5.0)
All	54	65	61	15	74	78	65	27	439	(99.9)

[a] January-July [b] New communities first inhabited in 1954-56

The attack rate in Léopoldville for this epidemic was 28.6 per 100 000 (99 cases in 346 000 population). If children under 5 years old only are considered, however, the incidence becomes 129 per 100 000 (98/76 200). The peak age-specific incidence was in 1-year-olds, where 344 per 100 000 (57/16 600) were affected. If estimated type-1 susceptibles only are considered, the attack rate in this age-group was an astonishing 445 per 100 000 (57/12 800)—a figure which does not take account of the possible protective effect of the live-virus vaccine which was given to 65% of 1-year-olds (Table 3).

In order to confirm the diagnosis of paralytic poliomyelitis, 55 of the cases reported during the epidemic were examined by us. In 50 of the patients, unequivocal flaccid paralysis or paresis was demonstrated, usually accompanied by muscular atrophy and hyporeflexia; whereas in four instances, no such changes were found. Inasmuch as the examinations were conducted several months after the onset of acute illness and no attempt was made to do detailed muscle testing, these cases may represent recovered paralytic poliomyelitis. In only one case (an unvaccinated child) was it our impression that the illness was unrelated to poliomyelitis (brachial plexus injury?); this case was eliminated from consideration. In addition, 29 hospital records were checked, and in all a clinical diagnosis of poliomyelitis seemed justifiable.

Of the 99 cases in the epidemic, 89 occurred in non-vaccinated and 10 in vaccinated individuals. The predominance of cases in non-vaccinated children was true in all geographical subdivisions of Léopoldville (Table 13). The details of the 10 vaccinated cases are given in Table 14, from which it can be seen that the age distribution and clinical characteristics of the cases were roughly typical of those found in the epidemic as a whole (Tables 10 and 11).

The interval between vaccination and the onset of illness was two months or more in seven of the 10 vaccinated individuals, whereas in three cases illness followed vaccination within 20 days. In patient No. 63, illness began one or two days after the administration of CHAT. In patient No. 81, illness is said to have begun six days after vaccination; however, when the child was seen two days later, she was already afebrile, suggesting the possibility that illness may actually have begun at an earlier date than 6 February. The third case (No. 93) occurred 20 days after vaccination. This is the minimal interval which could be derived from the history and is perhaps one or two days less than the actual interval.

TABLE 13

CHAT-VIRUS VACCINATION STATUS OF 1958-59 LÉOPOLDVILLE EPIDEMIC POLIOMYELITIS CASES

District	Vaccinated	Non-vaccinated	Total
Nouvelle Cité	2 [a]	47	49
Ancienne Cité	4	29	33
Bandalungwa	2	4	6
Ndjili	1	3	4
Matete	—	4	4
Kintambo	1	1	2
Camp Léopoldville	—	1	1
All	10	89	99

[a] Cases Nos. 63 and 81 in Table 14, which may have been in incubation period when vaccinated.

Stool specimens from 38 patients with paralytic disease were submitted to the laboratory of the Wistar Institute, Philadelphia, or to the laboratory of Dr M. Vandeputte at the Institut de Médecine tropicale Princesse Astrid in Léopoldville. At the Wistar Institute the stools were inoculated into monkey kidney tissue culture, while Dr Vandeputte used HeLa cell tissue culture and suckling mice. The results are combined in Table 15, from which it can be seen that 33 agents were recovered: 31 polioviruses and 2 Coxsackie viruses. Seven of the polioviruses isolated in Léopoldville were identified only by the morphological character of their cytopathogenic effects in tissue culture, whereas 24 were identified serologically: 21 were type 1 viruses, two were type 2, and one was type 3. The patients from whom type 1 isolations were made were distributed throughout the city; however, four of the five viruses which were definitely not type 1 poliovirus were from patients living in the Nouvelle Cité. Type 1 poliovirus was isolated in cases occurring in each month from October through March; the type 2 polioviruses were isolated in February and in April; and the type 3 poliovirus and Coxsackie virus isolations were both made in December.

Type 1 poliovirus was isolated from the stools of six vaccinated patients (Table 14). A seventh vaccinated patient (No. 14B) had complement-fixing antibodies for both types 1 and 2 poliovirus, but neutral-

TABLE 14

PARALYTIC POLIOMYELITIS IN INDIVIDUALS WHO HAD BEEN FED LIVE-VIRUS VACCINE PREVIOUS TO THE ONSET OF ILLNESS

Patient No.	Age (years or months)	Date of vaccination (1958-59)	Date of onset of illness (1958-59)	Interval vaccination to onset (months or days)	Extent of paralysis	Faecal Virus [a]	C-F test [b] Poliovirus type: 1	2	3
14B	2 y.	18 Aug.	20 Nov.	3 m.	Right leg	Not tested	+ (+	+ 0	0 0) [c]
62	1 y.	20-30 Sept.	6 Jan.	3 m.	Right leg	Not tested			
63	1 y.	9 or 10 Jan.	11 Jan.	1-2 d.	Both legs	Type I polio			
77	20 m.	22-27 Sept.	24 Jan.	4 m.	Left leg	Type I polio	+	0	0
81	15 m.	2 Feb.	8 (?) Feb.	6 d.(or less)	Left leg	Type I polio			
89	9 m.	5 Dec.	6 Feb.	2 m.	All 4 limbs	Type I polio	+	0	0
92	15 m.	5 Dec.	25 Feb.	2½ m.	Right leg	Not tested			
93	1 y.	6 Feb.	26 Feb.	20 d.	Left leg	Type I polio	+	0	0
99	11 m.	17 Jan.	14 Mar.	2 m.	Left leg	Type I polio			
101	2 y.	21 Jan.	22 Mar.	2 m.	Legs and arm	Not tested			

[a] Stools obtained within 1-2 weeks of date of onset.

[b] Complement-fixation test on sera obtained within 1-2 weeks of date of onset. Tests were performed by Dr Klaus Hummeler, using heated type-specific antigens.

[c] Neutralization test in tissue culture.

izing antibodies to type 1 only. The other 15 type 1 isolations were from non-vaccinated patients. Studies of the genetic and serological characters of these strains are reported below.

Evolution of the epidemic

In order to study the evolution of the epidemic, the cases of poliomyelitis were assigned a probable date of infection, which was the day of reporting

TABLE 15

VIRUS ISOLATIONS FROM FAECES OF PARALYTIC POLIOMYELITIS PATIENTS IN THE ACUTE STAGE OF ILLNESS [a]

District in which patient lived	Number of stools	Virus isolations: Poliovirus type: 1	2	3	Not typed [b]	Coxsackie [c]	None
Ancienne Cité	11	8	1	—	1	—	1
Nouvelle Cité	18	8	1	1	3	2	3
" Five Districts "	9	5	—	—	3	—	1
Totals	38	21	2	1	7	2	5

[a] Combined data of isolations made in Philadelphia, using monkey kidney tissue culture, and in Léopoldville, using HeLa cell tissue culture and suckling mice.

[b] Not typed serologically but identified as poliovirus by morphological effect on HeLa cells.

[c] Identified by histological effects on suckling mice; not typed.

TABLE 16

PARALYTIC POLIOMYELITIS CASES IN LÉOPOLDVILLE BY PROBABLE WEEK OF INFECTION

Weeks beginning	Districts								Cumulative total
	Ancienne Cité	Nouvelle Cité	Bandalungwa	Ndjili	Matete	Kintambo	Camp Léopoldville	All	
1958 Aug. 18, 25	—	—	—	—	—	—	—	—	—
Sept. 1	—	1	—	—	—	—	—	—	1
8, 15, 22	—	—	—	—	—	—	—	—	1
29	—	—	—	—	1	—	—	1	2
Oct. 6	—	—	—	—	—	—	—	—	2
13	1	1	—	—	—	—	—	2	4
20	—	1	—	1	—	—	—	2	6
27	1	2	—	—	—	—	—	3	9
Nov. 3	1	1	1	—	—	1 [a]	—	4	13
10	—	1	—	—	—	—	—	1	14
17	2	5	—	—	—	—	1	8	22
24	1	6	—	—	—	—	—	7	29
Dec. 1	4 [b]	4	—	1	—	—	—	9	38
8	—	6 [b]	1	—	—	—	—	7	45
15	2	6	—	1	—	—	—	9	54
22	3	2	—	—	—	—	—	5	59
29	2	1 [a]	1 [a]	—	—	—	—	4	63
1959 Jan. 5	1	3	1	—	—	1	—	6	69
12	3	1	1 [a]	—	—	—	—	5	74
19	—	3	—	—	—	—	—	3	77
26	3	1 [a]	—	—	1	—	—	5	82
Feb. 2	2	—	1	1 [a]	—	—	—	4	86
9	2	1	—	—	—	—	—	3	89
16	2 [c]	—	—	—	—	—	—	2	91
23	—	1	—	—	2	—	—	3	94
Mar. 2	2 [a]	1	—	—	—	—	—	3	97
9	1 [a]	—	—	—	—	—	—	1	98
16, 23	—	—	—	—	—	—	—	—	98
30	—	1	—	.	—	—	—	1	99
Apr. 6-30	—	—	—	—	—	—	—	—	99

[a] One vaccinated case.
[b] One case in a child older than 3 years.
[c] Two vaccinated cases.

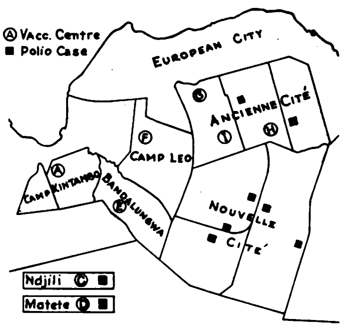
antedated by 14 days. The 14-day period was chosen because of two considerations: that the case reporting was remarkably prompt, usually within two days of the onset of paralysis; and that an incubation period of 12 days from infection to the first signs of paralysis appeared to be an acceptable estimate (Casey, 1942; Sartwell, 1952).

The paralytic poliomyelitis cases which occurred during the vaccination campaign in each district of Léopoldville are shown in Table 16 by probable week of infection. The epidemic appeared to begin at the end of October 1958. Nine patients, all unvaccinated, were infected before 1 November, and are represented in Fig. 3. Prior to 3 November, as shown in Table 2, no vaccine had been given in the Nouvelle Cité, and only 433 children had been vaccinated in the Ancienne Cité.

The first patient with poliomyelitis after the commencement of vaccination in Léopoldville was presumably infected in the Nouvelle Cité during the first week in September (Table 16). There was no known contact between this child and vaccinated subjects from other districts. The second paralysed child, also unvaccinated, lived in Matete and developed infection four weeks after vaccination had started in that district. A week before the first use of vaccine in the Ancienne Cité, on 20 October, the third Léopoldville case became infected. Eight weeks after the first CHAT virus had been administered in Ndjili, a child living in that district became the fourth Léopoldville case. A case developed in the Nouvelle Cité in the week of 13 October, followed by three more during the following two-week period (20 October–1 November). The second paralysed child in the Ancienne Cité (ninth Léopoldville case) was apparently infected during the second week of vaccination in that district, when only 433 children had received vaccine. This paralysed child lived 600 m from the nearest vaccination centre. The chronological relationships of vaccination to the first poliomyelitis cases in the Nouvelle and in the Ancienne Cités are also shown in Fig. 4 and 5 respectively.

FIG. 3

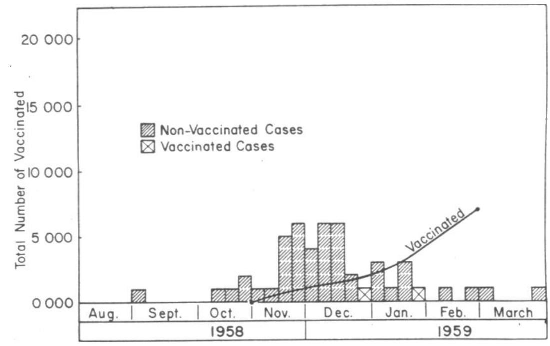
LOCATION OF CASES OF PARALYTIC POLIOMYELITIS OCCURRING IN LÉOPOLDVILLE BETWEEN BEGINNING OF VACCINATION CAMPAIGN ON 18 AUGUST 1958 AND 1 NOVEMBER 1958 [a]



[a] Also shown are the sites where vaccination was carried out during the same period. The numbers vaccinated at each centre and the weeks of vaccination are given in Table 2. The actual locations of Ndjili and Matete, shown inset, may be ascertained by reference to Fig. 1, on p. 206 of this issue, of the article by Lebrun et al.

FIG. 4

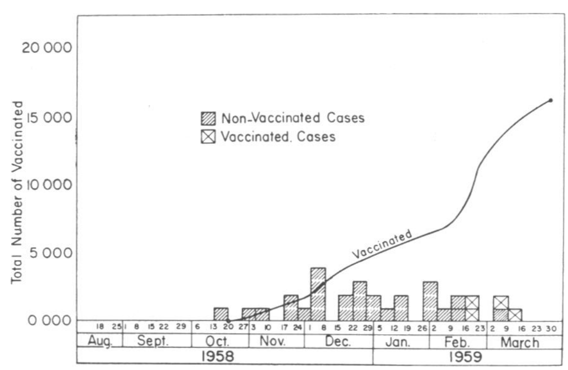
VACCINATIONS AND POLIOMYELITIS CASES IN NOUVELLE CITÉ [a]



[a] The cumulative total of vaccinated individuals in the Nouvelle Cité is indicated against the background of the cases of paralytic poliomyelitis which occurred during the same period. The week in which a case is placed is the week of presumed infection (see text).

FIG. 5

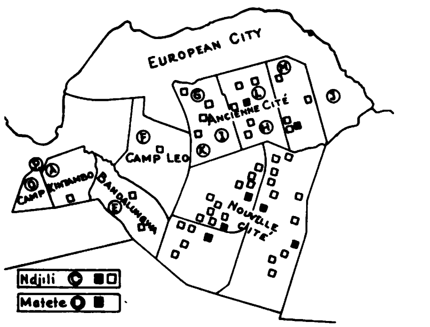
VACCINATIONS AND POLIOMYELITIS CASES IN ANCIENNE CITÉ [a]



[a] The cumulative total of vaccinated individuals in the Ancienne Cité is indicated against the background of the cases of paralytic poliomyelitis which occurred during the same period. The week in which a case is placed is the week of presumed infection (see text).

FIG. 6

LOCATION OF CASES OF PARALYTIC POLIOMYELITIS OCCURRING IN LÉOPOLDVILLE BETWEEN BEGINNING OF VACCINATION CAMPAIGN ON 18 AUGUST 1958 AND 21 DECEMBER 1958 [a]



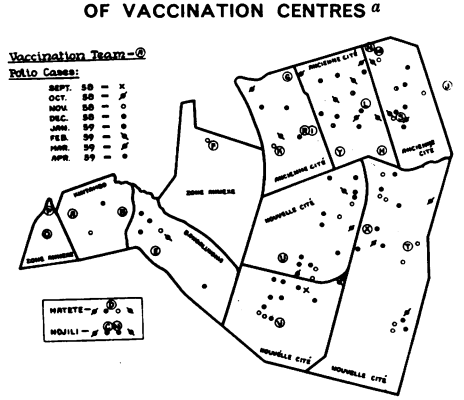
[a] The cases shown in Fig. 3 are represented by black squares and those occurring after 1 November by white squares. Also shown are the sites where vaccination was carried out during the same period. The numbers vaccinated at each centre and the weeks of vaccination are shown in Table 2.

The situation at the peak of the epidemic is shown in Fig. 6. From 3 November through 21 December, 46 cases of paralytic poliomyelitis developed: 29 in the Nouvelle Cité, 10 in the Ancienne Cité, and 6 elsewhere in Léopoldville (Table 16). An increased incidence of paralytogenic infections can be seen first late in October, principally in the Nouvelle Cité.

There were 45 more patients infected from 22 December 1958 through March 1959; they were generally distributed throughout Léopoldville (15 in the Nouvelle Cité; 21 in the Ancienne Cité; and 9 in the other districts). The locations of all of the cases and of the vaccination centres are depicted in Fig. 7. Inspection of this map, with reference to Table 2 for the dates of vaccination at each centre, reveals no clustering of cases around vaccination sites. The apparent clusters near centres S and U lose significance when it is seen that most of the cases had their onsets before vaccination was performed at those centres in February and March (Table 2).

FIG. 7

LOCATION OF ALL CASES OF PARALYTIC POLIOMYELITIS OCCURRING AMONG AFRICANS IN LÉOPOLDVILLE DURING 1958-59 EPIDEMIC AND SITES OF VACCINATION CENTRES [a]



[a] If Table 2 is consulted for the dates of vaccination at each centre, it will be seen that there was no relationship between cases of poliomyelitis and vaccine administration.

The frequency of intimate contact of subsequently paralysed children with vaccinees was of interest. For 66 of the epidemic cases (61 non-vaccinated and 5 vaccinated) information was available as to the vaccination status of siblings. As seen in Table 17, only four (two vaccinated and two non-vaccinated) of the 66 patients, or 6%, had vaccinated siblings.

RESULTS OF COMPARATIVE TESTS FOR GENETIC MARKERS OF THE TYPE 1 VIRUSES ISOLATED FROM VACCINATED INDIVIDUALS

Comparative studies of some genetic and immunological markers (Vogt et al., 1957; Lwoff, 1959; Benyesh-Melnick et al., 1959) were performed on viruses isolated from vaccinated and from non-vaccinated patients, and on human intestinal passage strains of CHAT virus. The results, which are given in detail in the paper by Koprowski and co-authors on page 243 of this issue, are summarized in Table 18, which shows that four strains isolated from vaccinated cases (including patients Nos. 81 and 93) and six strains from non-vaccinated patients had the *d*+/hot/MS+ characteristics of virulent virus, in contrast to CHAT virus and to strains isolated after 1-3 passages of CHAT, which remained *d*/cold/MS. In addition, when tested serologically, the strains

TABLE 17

VACCINATION HISTORY OF SIBLINGS OF LÉOPOLDVILLE POLIOMYELITIS CASES

Vaccination status of poliomyelitis case	Vaccination status of siblings		
	Vaccinated	Non-vaccinated	Total
Vaccinated	2	3	5
Non-vaccinated	2	59	61
Total	4	62	66

TABLE 18

GENETIC MARKERS AND SEROLOGICAL IDENTITY OF TYPE 1 POLIOVIRUSES ISOLATED FROM PATIENTS WITH PARALYTIC POLIOMYELITIS IN LÉOPOLDVILLE, IN COMPARISON WITH THE CHAT ATTENUATED STRAIN AND ITS HUMAN INTESTINAL PASSAGES

Category of strains	Strain	Age of patient (months)	District of residence	Date of onset (1958-59)	Genetic markers [a]	Plaque formation under anti-CHAT serum [b]
Isolated from unvaccinated patients	4	12	Ancienne Cité	23 Oct.	Hot, MS+	Yes
	7	8	Ndjili	30 Oct.	MS+	
	22	21	Camp Léopoldville	24 Nov.	MS+	
	40	6	Ancienne Cité	14 Dec.	MS+	
	90	16	Ancienne Cité	19 Feb.	Intermediary, *d*+, MS+	Yes
	94	13	Ancienne Cité	20 Feb.	Hot, MS+	Yes
Isolated from patients previously fed CHAT virus	81	15	Nouvelle Cité	8 Feb.	Hot, *d*+, MS+	
	89	9	Ndjili	6 Feb.	Hot, *d*+, MS+	Yes
	93	12	Ancienne Cité	26 Feb.	Hot, MS+	Yes
	99	11	Ancienne Cité	14 March	Hot, MS+	Yes
Virulent control	Mahoney	—	—	—	Hot, *d*+, MS+	Yes
Attenuated vaccine	CHAT	—	—	—	Cold, *d*, MS	No
1st-3rd human passages of CHAT virus [c]		—	—	—	Cold (10), Intermediary, (1), *d* (5), MS (11)	No (3)

[a] Hot = grows equally well in tissue culture at 40°C and at 37°C; Intermediary = grows at 40°C and at 37°C, but with a much higher titre at 37°C; Cold = grows poorly at 40° C; MS+ = forms plaques as well in monkey kidney stable line culture as in primary monkey kidney; MS = plaque formation inhibited in established monkey kidney tissue culture; *d*+ = forms plaques under acid agar as well as under alkaline agar; *d* = formation of plaques under acid agar delayed in comparison with that under alkaline agar.

[b] See Table 3 of article by Koprowski et al. on p. 247 of this issue.

[c] See Table 2 of article by Koprowski et al. on p. 245 of this issue

from the paralysed patients, both vaccinated and non-vaccinated, resembled the Mahoney virus in that plaque formation occurred in the presence of CHAT antisera, while the CHAT virus and its passage strains were completely inhibited in this respect (see the papers by Gard and by Koprowski et al. on pages 235 and 243).

ESTIMATES OF PROTECTION AGAINST POLIOMYELITIS PRODUCED BY THE CHAT STRAIN

The circumstance of a poliomyelitis epidemic in Léopoldville provided us with an opportunity to estimate the protection afforded by attenuated virus vaccination.

With respect to the relationship between vaccination and epidemic paralytic poliomyelitis (Tables 2 and 16), the city could be separated into three distinct divisions: the Nouvelle Cité, where the epidemic was largely over before large-scale vaccination commenced; the Ancienne Cité, where the epidemic occurred *pari passu* with vaccination; and the five smaller districts in which a considerable amount of vaccination was done prior to the epidemic. Accordingly, these three divisions were evaluated separately for evidence of protective effect of the vaccine. Because all but two of the poliomyelitis cases occurred in children less than 3 years old, the evaluation was confined to that age-group.

Two methods were employed: in the first, the changing risks of vaccinated and unvaccinated populations were measured by means of person-time units of exposure; whereas in the second, the risk was assessed for each week and the observed and expected incidences in vaccinees compared.

The first method employed as the numerator the number of vaccinated and of unvaccinated cases in children 6 months through 2 years old which occurred from the commencement of vaccination in the particular district of Léopoldville (Table 16); and as the denominator the number of person-weeks exposure for the period starting with the first case occurring after vaccination and ending with the last case. For the calculation of person-weeks, the weekly totals of vaccinated infants 6 months through 2 years old, which are contained in Table 19, were utilized. The non-vaccinated exposure was obtained by subtracting the vaccinated person-weeks from the total number of person-weeks.[1]

The summary results of the calculation of rates of poliomyelitis are given in Table 20, in which protection of the vaccine against paralytic poliomyelitis was estimated to be 53% in the Ancienne Cité, 71% in the Nouvelle Cité, and 68% in the " five districts ". If the Nouvelle Cité is excluded (because vaccination in this district largely followed the epidemic), an estimate of 60% protection is obtained.

The second method of estimation of protection was suggested by Dr Sven Gard (1959). The risk of paralytic poliomyelitis was calculated for each week by dividing the number of cases infected during the week (Table 16) by the number of children aged 6 months through 2 years living in the particular district (Table 1). This risk was then multiplied by the total numbers vaccinated up to the week in question (Table 19). The product gave the expected number of vaccinated cases during one week, and by addition of the weekly figures, the total expected number of cases in vaccinees was obtained.[2]

TABLE 19

CUMULATIVE NUMBERS OF VACCINATED CHILDREN 6 MONTHS THROUGH 2 YEARS OLD (IN THOUSANDS)

Week beginning	Geographical division		
	Ancienne Cité	Nouvelle Cité	Five districts
1958 Sept. 22	—	—	4.9
29	—	—	4.9
Oct. 6	—	—	5.4
13	—	—	5.4
20	0.1	—	5.4
27	0.2	—	5.4
Nov. 3	0.6	0.1	5.5
10	0.7	0.1	5.5
17	0.9	0.2	5.5
24	1.1	0.3	5.6
Dec. 1	1.5	0.5	5.6
8	2.0	0.7	6.0
15	2.5	0.8	6.1
22	2.6	0.9	6.1
29	2.8	1.1	6.1
1959 Jan. 5	2.9	1.1	6.2
12	3.0	1.2	6.2
19	3.5	1.7	6.4
26	3.7	1.9	6.4
Feb. 2	4.1	2.6	6.5
9	4.9	2.9	6.5
16	6.6	3.3	6.7
23	7.1	3.7	6.8
Mar. 2	7.8	4.2	7.0
9	8.3	4.6	7.0
16	8.7	5.0	7.2
23	9.2	5.3	7.2
30	9.6	5.6	7.4

[1] For example, in the Ancienne Cité, cases occurred in 4 vaccinated and 27 unvaccinated children in the susceptible age-group between 27 October and 15 March. The number of children in the same age-group vaccinated in that district rose from 200 to 8300 during the 20-week interval (Table 19). Calculating week by week, 64 800 vaccinated person-weeks of experience were acquired during that period. Inasmuch as there were 13 500 children 6 months through 2 years old in the Ancienne Cité (Table 1), the total experience was 270 000 person-weeks (13 500 × 20), and the unvaccinated experience 205 200 person-weeks (270 000 less 64 800).

[2] In mathematical terms, for each district:

$$\frac{\text{Polio}_W}{\text{Susc.}} (\text{Vacc.}) = \text{Exp}_W \; ; \; \Sigma \, \text{Exp}_W = \text{Exp}_T$$

where Polio_W = observed number of cases in a given week; Susc. = total number of susceptibles (population 6 months through 2 years old), Vacc. = cumulative number of vaccinees 6 months through 2 years old as of the given week ; Exp_W = expected number of cases in vaccinees during one week; and Exp_T = expected number of cases in vaccinees for total period.

For example, if one case occurred in a district in which there were 10 000 children in the susceptible age-group, of which 5000 had been vaccinated by the week of the case, then

$$\frac{1}{10\,000} (5000) = 0.5 = \text{Exp}_W.$$

TABLE 20
ESTIMATED PROTECTION AGAINST PARALYTIC POLIOMYELITIS BY CHAT-VIRUS VACCINATION IN LÉOPOLDVILLE AFRICAN CHILDREN 6 MONTHS THROUGH 2 YEARS OF AGE (PERSON-TIME METHOD)

Geographical division	Group	Cases [a]	Person-weeks [a]	Rate per 10^5 person-weeks	Estimated protection
Ancienne Cité	Vaccinated	4	64 800	6.2	53%
	Non-vaccinated	27	205 200	13.2	—
Nouvelle Cité	Vaccinated	2	47 800	4.2	71%
	Non-vaccinated	41	284 200	14.4	—
" Five districts"	Vaccinated	4	130 400	3.0	68%
	Non-vaccinated	13	133 600	9.7	—
Total	Vaccinated	8	—	4.6	60%
	Non-vaccinated	40	—	11.5	—

[a] For Ancienne Cité the period from 27 Oct. to 15 March; for Nouvelle Cité the period from 3 Nov. to 5 April; for " Five districts " the period from 29 Sept. to 1 March.

The results of the second method are given in Table 21. There were 8.35 cases expected in vaccinees in the Ancienne Cité, but only 4 occurred. Similarly, only 4 cases were seen in the " five districts ", despite a predicted number of 8.43. Among the vaccinated population of the Nouvelle Cité, 3.75 cases were expected, and 2 were observed (Patients Nos. 63 and 81 in Table 14), both of which developed within six days of vaccination. Inasmuch as any category should have at least 5 expected units for a χ^2 test, the Nouvelle Cité data were eliminated. Using only the figures from the Ancienne Cité and the " five districts ", 16.78 cases would be expected in vaccinees (assuming that the vaccine was ineffectual), but 8.0 cases were actually observed ($\chi^2=4.61$; $n=1$; $P=<0.05$). Thus it can be stated with 95% confidence that there was a real difference between the expected and the observed numbers of cases of poliomyelitis in CHAT-vaccinated African children.

DISCUSSION

More than 95% of cases of paralytic poliomyelitis among Africans in Léopoldville occur within the first five years of life (see the preceding article, page 203). From this fact one could predict that antibodies to poliovirus would be absent only in very young Africans, and that by five years of age almost all children would be sero-immune. This prediction was confirmed by the results of our serological survey. These data are also in agreement with previous epidemiological studies of poliomyelitis in the tropics. For example, in Cairo, Egypt, and in French Morocco, Paul et al. (1952), and Paul & Horstmann (1955) found that natural infection and immunization by poliovirus occurred regularly during the first five years of life, a fact which was reflected by the almost total concentration of paralytic disease in that young age-group. The age at which 50% of sera had neutralizing antibodies to any of the types of poliomyelitis virus was approxim-

TABLE 21
SIGNIFICANCE OF ESTIMATED PROTECTION AGAINST PARALYTIC POLIOMYELITIS BY CHAT-VIRUS VACCINATION IN LÉOPOLDVILLE AFRICAN CHILDREN 6 MONTHS THROUGH 2 YEARS OF AGE

Geographical division	Cases observed	Cases expected	χ^2
Ancienne Cité (A)	4	8.35	2.26
Nouvelle Cité (B)	2 [b]	3.25	— [c]
" Five districts " (C)	4	8.43	2.45
(A)+(C)	8	16.78	4.61 [d]
(A)+(B)+(C)	10	20.03	4.90 [d]

[a] After Gard (1959)
[b] Two cases may have been in incubation period of disease when vaccinated.
[c] No χ^2 calculated because expected number less than 5.
[d] $n = 1$; $P = <0.05$.

ately 2 years in Cairo and Casablanca, whereas in Léopoldville this point was reached in the 3-year-old group. In this respect the serological status of Liberians or of Southern Louisiana Negroes as reported by Gelfand & Miller (1956) appeared to be closer to the situation in Léopoldville. Previous serological studies of Africans in the Belgian Congo have given similar results (Barski & Lépine, 1956; Pattyn et al., 1957).

The remarkably high epidemic attack rates for paralytic poliomyelitis in Léopoldville African infants (344 per 100 000 in 1-year-olds) is of interest in the light of the suggestion by Paul et al. (1952) that the over-all incidence of poliomyelitis is as high in the tropics as in temperate climates despite the limitation of the disease to the young child. During the 8½ months of heightened surveillance generated by the vaccination campaign the incidence of paralytic poliomyelitis in Léopoldville was 28.6 per 100 000; this projected over a full year would be 20.3 per 100 000. In the USA in 1955, prior to the widespread use of killed-virus vaccine, the incidence was 8.4 per 100 000. The co-existence of high rates for paralytic poliomyelitis and high, though improving, rates of infant mortality (see page 206), is interesting in view of the rough inverse correlation between these two statistics which has been observed in non-tropical countries (Payne, 1955).

The evidence relative to safety of the CHAT strain presented here was of two types: direct and indirect. The direct evidence consisted of the clinical observations made on 7200 vaccinated children, and the indirect evidence was derived from the study of poliomyelitis in Léopoldville since the beginning of the campaign. The principal objective of the post-vaccination inquiries was the detection and study of serious illnesses which might be reactions to vaccination. No neurological illnesses were found which could be attributed to infection by poliomyelitis virus.

The routine recording of all complaints, however minor, led to the accumulation of data on minor illnesses. There was a significantly greater incidence of total illnesses during the fifteen days after vaccination than in the seven days just preceding it; but this difference was also evident for types of illness such as upper respiratory infection, which would seem *a priori* to be unrelated to poliovirus infection. Thus the implication is that the post-vaccination and pre-vaccination inquiries were not made in comparable population samples. In fact, there are reasons why the population coming for vaccination must have been selected for good health. Children who were recently ill would probably not have been brought by their mothers for vaccination; in addition, children who were ill when brought for vaccination were rejected by the vaccinators. If during the next fifteen days after virus feeding the children suffered a " usual " amount of intercurrent illness, an apparent increase in disease would result. On this basis, one would expect that the percentages of illness found on the 8-day and 15-day post-vaccination visits would be the same; whereas if illnesses were caused by the vaccine, the incubation period would probably cause an increased number during the second post-vaccination week. The incidence of illness was observed to be the same during the second week after ingestion of the virus as during the first.

Another factor of importance in evaluating the significance of these data is the accuracy of the answers volunteered by the mothers. It was the impression of the interviewers that the largely uneducated mothers sometimes ignored and sometimes exaggerated minor illnesses. In summary, these post-vaccination inquiries were important not as evidence relating to the presence or absence of minor reactions to living virus vaccination, but rather as an indication of the care with which the investigation for major reactions was conducted.

The estimation of the numbers of susceptible individuals subjected to live-virus vaccination was of considerable importance with regard to the evaluation of safety. The estimates had to take into account the serological status of the population at the time of feeding and the percentage of vaccinees actually infected by the attenuated virus, in addition to the gross totals of people fed virus. Two additional factors which complicated the estimation of vaccinated susceptibles were, first, the unknown serological status of infants under 6 months of age, and, secondly, the decrease in type-1 susceptibles produced by the epidemic virus and by spread of attenuated virus. However, these two effects are thought to cancel each other.[1]

[1] If maternal antibody titres in the cord bloods of the infants were randomly distributed and lost at a constant rate, then in view of the low immunity of 6-month-old infants (Table 4) the average seronegativity of infants under 6 months was at least 50%. Thus 3800 of such vaccinated infants may have been susceptible. On the other hand, if it can be assumed that there were 35% fewer susceptibles among the children vaccinated after 1 February (the approximate date on which the second blood specimens were taken from non-vaccinated individuals, which was also after the peak of the epidemic), then 4000 susceptibles should be subtracted from the total vaccinated.

If the figures in Tables 3 and 6 are accepted as the best estimates possible, then over 13 000 type-1 negatives and 7200 triple negatives were vaccinated and probably infected (21 800 × 60%). In addition, 2000 type-1 negatives and 1300 triple negatives were directly observed for reactions to vaccination.

The fact that an epidemic followed the use of living virus requires careful evaluation. It appears certain that the epidemic was due to type 1 poliovirus, which was isolated from the stools of patients in the acute stage of paralytic illness in 21 of 26 (81%) cases in which a faecal virus was specifically identified. This percentage was much greater than the 1.7% type 1 carriers which were found among healthy children in Léopoldville (see page 203); and the frequent combination of paralytic disease and positive carriage of type 1 poliovirus made a relationship between the two probable.

Evidence was presented that the age distribution and localization of paralysis of the patients in this epidemic were substantially the same as in previous years; but that in contrast to past years the epidemic had a higher incidence in the Nouvelle Cité than in the Ancienne Cité. It is conceivable that this reversal was the result of the more extensive live virus vaccination performed in the Ancienne Cité, although a fortuitous variation of the disease is perhaps as likely an explanation.

In reviewing the onset of the epidemic, it was shown that none of the nine cases of poliomyelitis occurring before 1 November was in vaccinated children, and that seven of the nine patients were unlikely to have had contact with the CHAT virus. In both the Nouvelle and the Ancienne Cités the first cases preceded the use of vaccine, and the later cases were not related geographically to the sites of vaccination. The family history of the cases revealed contact with a vaccinated sibling in only 3% of families in which the paralysed child was not vaccinated; a percentage which does not seem excessive in view of the vaccination of over 50% of children less than 5 years old by the end of the epidemic (week of 30 March).

The genetic and serological identification of the viruses isolated from patients was significant with regard to the possibility that the two cases in which the intervals between vaccination and onset of illness were 6 and 20 days were vaccine-caused. The type 1 strains isolated from these patients were *d*+/hot/MS+, whereas the CHAT strain and its experimentally observed human passage strains were *d*/cold/MS. Even more significant was the clear serological distinction between the strains recovered from the two above-mentioned patients and the attenuated strains. In addition, these two viruses were found to resemble type 1 strains recovered from non-vaccinated paralysed patients. The latter strains also could be differentiated from the CHAT strains. These studies are documented in detail in the following communications by Gard and by Koprowski et al.

Thus, the lack of chronological or geographical association of cases, the lack of their association with vaccination centres or with contact with vaccinated individuals, and the characteristics of the causative viruses provided no positive evidence for a relationship between the vaccine virus and the epidemic, and indicated that the latter was a fortuitous occurrence. In this connexion, it might be pointed out that since 1951 the average interval between epidemic peaks of poliomyelitis in Léopoldville was twelve months (see the preceding article). The peak of the 1958-59 epidemic followed the previous one by just twelve months.

The low serological response to vaccination was surprising, considering the results obtained with the CHAT strain both in small carefully controlled groups (Plotkin et al., 1959) and in field studies (Przesmycki et al., 1959) using exactly the same pool of virus material as was used in Léopoldville. In these studies the serological efficacy of the CHAT strain was 90%-95%. The explanation for this disparity in results is obscure. It appears unlikely that loss of virus titre under tropical conditions was at fault, inasmuch as titration of vaccine samples returned to Philadelphia showed good stability, as discussed in the preceding article. Faulty administration also seems ruled out, since at least the first 10 000 vaccinations were carefully observed but the responses of these children were not better than the general experience. The most attractive explanation is based on the interfering effect of wild enteric virus infection on the response to attenuated virus which has been recently demonstrated by several groups (Gelfand et al., 1959; Paul et al., 1959; Sabin, 1959; and Benyesh-Melnick et al., 1959). Coxsackie, Echo, and heterotypic polioviruses have all been implicated in interference with the response to live poliovirus vaccine. For example, Benyesh-Melnick et al. (1959) found that the excretion of wild enteric virus at the time of feeding in a group of seronegative Mexican children was associated with a lack of response to the vaccine virus. Thus, only 11 of 40 (28%) children excreting wild viruses developed homotypic antibodies to the attenuated poliovirus, in contrast to 20 of 22 (91%) children who were not carriers of wild virus. As in other tropical cities, enteric viruses are in constant circulation in Léopoldville, as can be proven by virus isolations from the stools of healthy children. Using HeLa and human amnion tissue culture cells and suckling mice, Vandeputte [1] isolated enteric viruses from 37% of 1200 faecal specimens which were obtained over a twelve-month period. Undoubtedly, if other tissue culture lines had been used, recoveries of ECHO viruses and miscellaneous agents would have increased the number of positive stools. Thus the conditions in Léopoldville are favourable for the occurrence of interference.

The low rate of sero-conversion in this trial raises the question whether circulation of enteric viruses may pose a serious problem for a successful campaign with living attenuated virus vaccination in certain areas of the world. The role of increased dosage or of repeated administration of virus in overcoming interference has not been explored. Moreover, if further studies show that vaccination of infants less than six months of age (who might have less opportunity than their more mobile siblings for infection by enteric viruses) is more successful than vaccination of older age-groups, the solution to this problem would be the inclusion of live virus administration in medical examinations just after birth or early in life.

What part of the 60% sero-conversion should be attributed to infections by wild type 1 virus or to contact infections from vaccinated siblings appears impossible to estimate. The timing of the bleedings was such that most of the post-vaccination specimens were obtained before the onset of widespread natural infection, as confirmed by the similarity of the pre-vaccination sero-determinations obtained early in November to those done in August. In contrast, all the re-bleedings of non-vaccinated children were obtained at the end of January, after the peak of the epidemic, and therefore presumably reflected the recent prevalence of wild type 1 viruses. Moreover, the low rates of seroconversion noted in vaccinees implies that spread of virus was not extensive, since if spread had occurred frequently, vaccinated children (who were most likely to be in contact with other vaccinees) would have shown a higher percentage of " takes ".

Although there are admittedly manifold difficulties in measuring attack rates in an epidemic where the vaccinated population is continuously increasing and where the susceptibles are decreasing, the absence of other published estimates of protection suggested that this opportunity should be utilized as fully as possible. The two methods employed to evaluate protection both have defects. The calculation of person-weeks of exposure is advantageous in taking into account the shift in numbers from the vaccinated to the unvaccinated population, but it has the defect of not compensating for the change in risk as an epidemic waxes and wanes. For this reason, the final estimate was made after exclusion of the Nouvelle Cité, in which the major risk was judged to have passed before a significant proportion of the population was vaccinated. A better estimate could be based on the " five districts ", in which 41% of the susceptible population was vaccinated prior to the first case of poliomyelitis, and on the Ancienne Cité, in which poliomyelitis occurred at a relatively high incidence until well into February. It is of great interest to speculate that the estimate of 60% protection against poliomyelitis, and the observed antibody response of 60%, may imply that the cases in vaccinated individuals were examples of failure of the virus feeding to produce an intestinal infection and antibody response.

The second method, which compared observed and expected numbers of vaccinated cases, corrected for the changing risk by treating each week separately. However, because the total population rather than the unvaccinated population was used in the calculation of the expected rate of poliomyelitis in the vaccinees, this method probably underestimates the extent of protection. Nevertheless, a statistically significant protective effect could be attributed to the vaccine.

It should be noted that although the degree of spread of attenuated virus to non-vaccinated individuals was not established precisely, whatever spread took place must have decreased the estimates of effectiveness by decreasing the number of non-vaccinated susceptibles.

In summary, by two methods of calculation and in spite of the inclusion of biases against the demonstration of protection, the vaccine appeared effective. Further observations in Léopoldville and in other areas where large-scale vaccination with living attenuated poliovirus has been performed are necessary to provide more clear-cut data concerning the mechanism and extent of protection.

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[1] See the article on page 313 of this issue.

Since the submission of this article, poliomyelitis data from Léopoldville have been collated for an additional period: 1 May to 30 September 1959. During this time, there have been 32 cases of paralytic illness in the age-group 6 months to 3 years old (10 in vaccinated and 21 in non-vaccinated individuals), while the number of vaccinated children in that age-group reached approximately 35 300. The addition of the new information increases the estimate of protection determined by the person-time method to 66%. The χ^2 value computed by the adjusted risk method becomes 11.91, which reduces the probability of the observation having been made by chance to <0.01. Thus the observed facts continue to be consistent with the hypotheses advanced.

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RÉSUMÉ

La souche CHAT de virus poliomyélitique atténué de type 1 a été administrée à des enfants et nourrissons africains de Léopoldville (Congo belge) (voir page 203 de ce numéro).

L'étude sérologique de nourrissons et d'enfants africains a démontré que, si l'immunisation naturelle contre la poliomyélite était pratiquement achevée à l'âge de 5 ans, un fort pourcentage des enfants de moins de 3 ans étaient encore sensibles à la maladie.

A la fin d'avril 1959, du virus CHAT avait été administré à environ 46 000 enfants de moins de cinq ans. On estime que 21 800 étaient négatifs au type 1 et 12 100 étaient négatifs aux trois types avant vaccination.

Quelque 3400 enfants africains sensibles au type 1 et âgés de moins de cinq ans, dont 2100 étaient triplement négatifs, ont reçu de la souche CHAT et ont été suivis, par des visites à domicile, après la vaccination. Aucun d'eux n'a présenté de poliomyélite paralytique ou de méningite aseptique.

Deux à trois mois après la vaccination, ces enfants ont fait l'objet de prélèvements de sang; 60% de ceux qui étaient préalablement négatifs au type 1 possédaient des anticorps. Ces résultats étaient anormalement faibles pour la souche considérée et, pour expliquer ce fait, on a supposé une interférence de la part de virus entériques naturels.

Deux mois environ après le début de la vaccination, une épidémie de type 1 a éclaté dans la population africaine. Bien que sévère, elle était semblable aux poussées antérieures du point de vue de l'âge des sujets, de la distribution des cas, des atteintes paralytiques et de l'intervalle écoulé depuis la précédente épidémie.

Cette épidémie s'est distinguée cependant par le fait qu'elle était concentrée dans une section de la ville. Aucune vaccination n'avait été pratiquée dans ce district. On n'a découvert aucune association géographique, chronologique ou familiale entre les sujets vaccinés et les cas poliomyélitiques. Sur les 99 cas de poliomyélite, 89 se sont produits chez des sujets non vaccinés et 10 chez des sujets vaccinés (en cours d'épidémie). A en juger d'après l'intervalle écoulé entre la vaccination et le début de l'attaque et d'après les caractéristiques des virus isolés chez les malades, aucun des cas apparus chez les vaccinés n'était provoqué par le vaccin. De même, les virus poliomyélitiques isolés chez des sujets non vaccinés différaient des virus atténués par des caractères sérologiques et génétiques.

La vaccination par les virus CHAT s'est révélée conférer une protection importante contre le virus épidémique de type 1. Cette protection a été estimée à 60%, ce qui est à peu près du même ordre de grandeur que le taux de séroconversion chez les vaccinés.

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